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(54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH ANTI-TUMOR ANTHRACYCLINE DERIVATIVES

(57) Abstract: The present invention is concerned with combinations of a farnesyl transferase inhibitor and an anthracycline derivative for inhibiting the growth of tumor cells and useful in the treatment of cancer.

FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH ANTI-TUMOR ANTHRACYCLINE DERIVATIVES

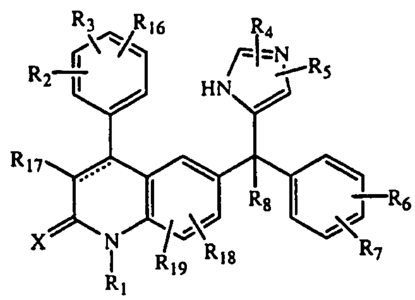
The present invention is concerned with combinations of a farnesyl transferase inhibitor and an anti-tumor anthracycline derivative for inhibiting the growth of tumor cells. and useful in the treatment of cancer.

Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer. A particular group of oncogenes is known as *ras* which have been identified in mammals, birds, insects, mollusks, plants, fungi and yeasts. The family of mammalian *ras* oncogenes consists of three major members ("isoforms") : H-*ras*, K-*ras* and N-*ras* oncogenes. These *ras* oncogenes code for highly related proteins generically known as $p21^{ras}$. Once attached to plasma membranes, the mutant or oncogenic forms of $p21^{ras}$ will provide a signal for the transformation and uncontrolled growth of malignant tumor cells. To acquire this transforming potential, the precursor of the $p21^{ras}$ oncoprotein must undergo an enzymatically catalyzed farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Therefore, inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, will prevent the membrane attachment of $p21^{ras}$ and block the aberrant growth of *ras*-transformed tumors. Hence, it is generally accepted in the art that farnesyl transferase inhibitors can be very useful as anticancer agents for tumors in which *ras* contributes to transformation.

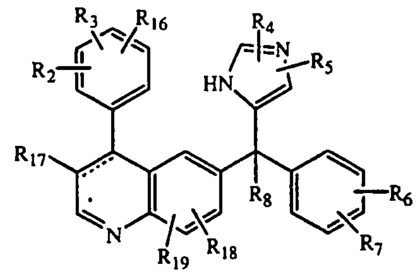
Since mutated, oncogenic forms of *ras* are frequently found in many human cancers, most notably in more than 50 % of colon and pancreatic carcinomas (Kohl et al., *Science*, vol 260, 1834 - 1837, 1993), it has been suggested that farnesyl tranferase inhibitors can be very useful against these types of cancer. Following further investigations, it has been found that a farnesyl transferase inhibitor is capable of demonstrating antiproliferative effects *in vitro* and antitumor effects *in vivo* in a variety of human tumor cell lines with and without ras gene mutations

WO-97/21701 describes the preparation,.formulation and pharmaceutical properties of farnesyl protein transferase inhibiting (imidazoly-5-yl)methyl-2-quinolinone derivatives

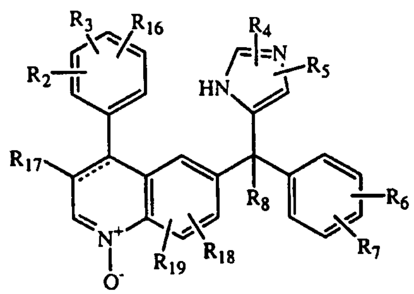
of formulas (I), (II) and (III), as well as intermediates of formula (II) and (III) that are metabolized in vivo to the compounds of formula (I). The compounds of formulas (I), (II) and (III) are represented by



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,
or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-S(O)$_2$-R^9,
wherein Alk^1 is C_{1-6}alkanediyl,
R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),
-O-CH_2-CH_2-O- (a-2),
-O-CH=CH- (a-3),
-O-CH_2-CH_2- (a-4),
-O-CH_2-CH_2-CH_2- (a-5), or
-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS$(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or
when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula
-O-CH_2-O- (c-1), or
-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula
-O-R^{10} (b-1),
-S-R^{10} (b-2),
-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

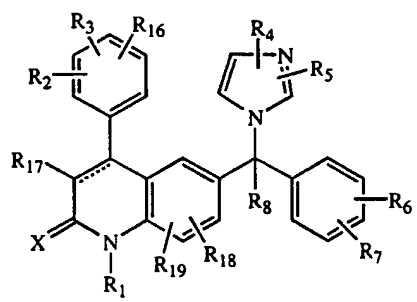
R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{19} is hydrogen or C_{1-6}alkyl;

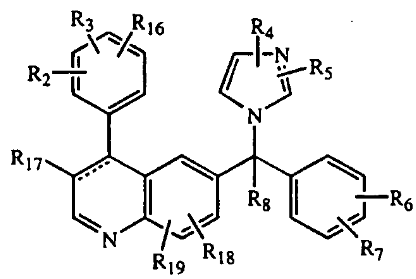
Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

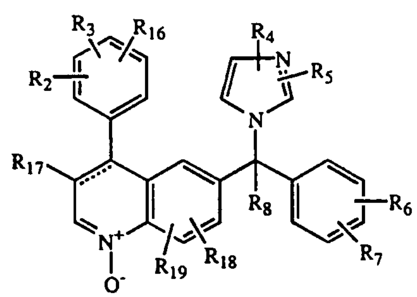
WO-97/16443 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IV), as well as intermediates of formula (V) and (VI) that are metabolized in vivo to the compounds of formula (IV). The compounds of formulas (IV), (V) and (VI) are represented by



(IV)



(V)



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-

aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,
or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$,
wherein Alk^1 is C_{1-6}alkanediyl,
R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, amino-C_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl; or
when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

$-O-CH_2-O-$	(a-1),
$-O-CH_2-CH_2-O-$	(a-2),
$-O-CH=CH-$	(a-3),
$-O-CH_2-CH_2-$	(a-4),
$-O-CH_2-CH_2-CH_2-$	(a-5), or
$-CH=CH-CH=CH-$	(a-6);

R^4 and R^5 each independently are hydrogen, Ar^1, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkyl$S(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy or Ar^2oxy;

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl-carbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy-carbonylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, Ar^1, Ar^2C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl;

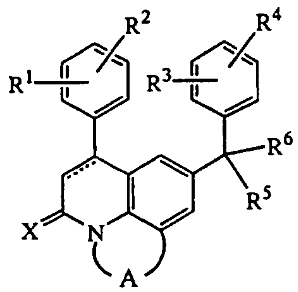
R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{11} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo;

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

WO-98/40383 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VII)



(VII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

$-CH=CH-$	(a-1),	$-CH_2-S-$	(a-6),
$-CH_2-CH_2-$	(a-2),	$-CH_2-CH_2-S-$	(a-7),
$-CH_2-CH_2-CH_2-$	(a-3),	$-CH=N-$	(a-8),
$-CH_2-O-$	(a-4),	$-N=N-$	(a-9), or
$-CH_2-CH_2-O-$	(a-5),	$-CO-NH-$	(a-10);

wherein optionally one hydrogen atom may be replaced by C_{1-4}alkyl or Ar^1;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^2, Ar^2-C_{1-6}alkyl, Ar^2-oxy, Ar^2-C_{1-6}alkyloxy; or when on adjacent positions R^1 and R^2 taken together may form a bivalent radical of formula

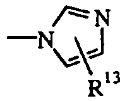
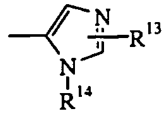
$-O-CH_2-O-$	(b-1),
$-O-CH_2-CH_2-O-$	(b-2),
$-O-CH=CH-$	(b-3),
$-O-CH_2-CH_2-$	(b-4),
$-O-CH_2-CH_2-CH_2-$	(b-5), or
$-CH=CH-CH=CH-$	(b-6);

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^3-oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R^3 and R^4 taken together may form a bivalent radical of formula

$-O-CH_2-O-$	(c-1),
$-O-CH_2-CH_2-O-$	(c-2), or

-CH=CH-CH=CH- (c-3);

R^5 is a radical of formula

 (d-1),  (d-2),

wherein R^{13} is hydrogen, halo, Ar^4, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{14} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^5, Ar^5-C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^7 (e-1),

-S-R^7 (e-2),

-N-R^8R^9 (e-3),

wherein R^7 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^6, Ar^6-C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{10} or -Alk-N$R^{11}R^{12}$;

R^8 is hydrogen, C_{1-6}alkyl, Ar^7 or Ar^7-C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^8, Ar^8-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^8-carbonyl, Ar^8-C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk-OR^{10} or -Alk-N$R^{11}R^{12}$;

wherein Alk is C_{1-6}alkanediyl;

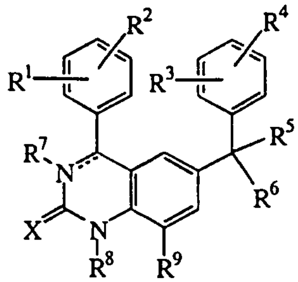
R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, Ar^9 or Ar^9-C_{1-6}alkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^{10} or Ar^{10}-C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, Ar^{11} or Ar^{11}-C_{1-6}alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

WO-98/49157 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VIII)



(VIII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^1C_{1-6}alkyl, Ar^1oxy or Ar^1C_{1-6}alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^{10} (a-1),

-S-R^{10} (a-2),

-N-$R^{11}R^{12}$ (a-3),

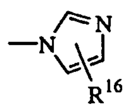
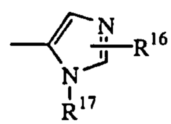
wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^1carbonyl, Ar^1C_{1-6}alkylcarbonyl, aminocarbonyl-

carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino,
or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;
wherein Alk is C_{1-6}alkanediyl;
R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;
R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;
R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^6 is a radical of formula

 (b-1),  (b-2),

wherein R^{16} is hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS$(O)_2C_{1-6}$alkyl;
R^{17} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^7 is hydrogen or C_{1-6}alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2CH_2 or Het^1CH_2;

R^9 is hydrogen, C_{1-6}alkyl , C_{1-6}alkyloxy or halo; or

R^8 and R^9 taken together to form a bivalent radical of formula

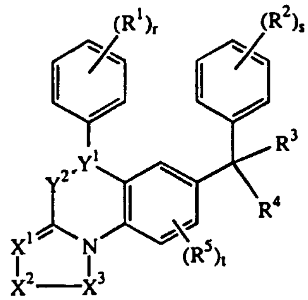
-CH=CH- (c-1),
-CH_2-CH_2- (c-2),
-CH_2-CH_2-CH_2- (c-3),
-CH_2-O- (c-4), or
-CH_2-CH_2-O- (c-5);

Ar^1 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl;

Ar^2 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

Het^1 is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

WO-00/39082 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IX)



(IX)

or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$=X^1-X^2-X^3-$ is a trivalent radical of formula

$=N-CR^6=CR^7-$	(x-1),	$=CR^6-CR^7=CR^8-$	(x-6),
$=N-N=CR^6-$	(x-2),	$=CR^6-N=CR^7-$	(x-7),
$=N-NH-C(=O)-$	(x-3),	$=CR^6-NH-C(=O)-$	(x-8), or
$=N-N=N-$	(x-4),	$=CR^6-N=N-$	(x-9);
$=N-CR^6=N-$	(x-5),		

wherein each R^6, R^7 and R^8 are independently hydrogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkyloxy, aryloxy, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxy-C_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, cyano, amino, thio, C_{1-4}alkylthio, arylthio or aryl;

$>Y^1-Y^2-$ is a trivalent radical of formula

$>CH-CHR^9-$	(y-1),
$>C=N-$	(y-2),
$>CH-NR^9-$	(y-3),or
$>C=CR^9-$	(y-4);

wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxyC_{1-4}alkyl, cyano, carboxyl, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, aryl;

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

each R^1 and R^2 are independently hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, aryl, arylC_{1-6}alkyl, aryloxy or arylC_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminocarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; or

two R^1 or R^2 substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula

$-O-CH_2-O-$	(a-1),
$-O-CH_2-CH_2-O-$	(a-2),
$-O=CH=CH-$	(a-3),
$-O-CH_2-CH_2-$	(a-4),
$-O-CH_2-CH_2-CH_2-$	(a-5), or
$-CH=CH-CH=CH-$	(a-6);

R^3 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonyl, hydroxycarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, aryl, arylC_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

or a radical of formula

$-O-R^{10}$	(b-1),
$-S-R^{10}$	(b-2),
$-NR^{11}R^{12}$	(b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl, arylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula $-Alk-OR^{13}$ or $-Alk-NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, aryl, hydroxy, amino, C_{1-6}alkyloxy, C_{1-6}alkylcarbonylC_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC_{1-6}alkylcarbonyl, arylC_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, mono- or di(C_{1-6}alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C_{1-3}alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, or a radical or formula $-Alk-OR^{13}$ or $-Alk-NR^{14}R^{15}$;

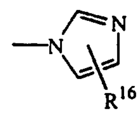
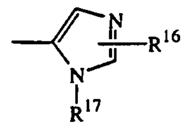
wherein Alk is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl or arylC_{1-6}alkyl;

R^4 is a radical of formula

 (c-1),  (c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, arylC_{1-6}alkyl, trifluoromethyl or di(C_{1-4}alkyl)aminosulfonyl;

R^5 is C_{1-6}alkyl , C_{1-6}alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

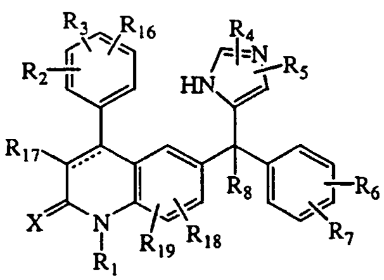
Anthracycline derivatives are important anti-tumor agents and comprise antibiotics obtained from the fungus *Strep. peuticus var. caesius* and their derivatives, characterised by having a tetracycline ring structure with an unusual sugar, daunosamine, attached by a glycosidic linkage. Among these compounds, the most widely used include daunorubicin, which has the chemical name 7-(3-amino-2,3,6-trideoxy-L-lyxohexosyloxy)-9-acetyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-4-methoxy-5,12-naphthacenequinone, doxorubicin, which has the chemical name 10-[(3-amino-2,3,6-trideoxy-alphaL-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-5,12-naphthacenedione, and idarubicin, which has the chemical name 9-acetyl-7-[(3-amino-2,3,6-trideoxy-alphaL-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione. Daunorubicin and idarubicin have been used primarily for the treatment of acute leukaemias whereas doxorubicin displays broader activity against human neoplasms, including a variety of solid tumors particularly breast cancer. However, anthracycline derivatives generally display a serious cardiomyopathy at higher doses, which limits the doses at which these compounds can be administered.

There is therefore a need to increase the inhibitory efficacy of anti-tumor anthracycline derivatives against tumor growth and also to provide a means for the use of lower dosages of anti-tumor anthracycline derivatives to reduce the potential of adverse toxic

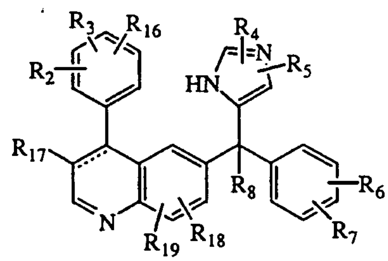
side effects to the patient.

It is an object of the invention to provide a therapeutic combination of an anti-tumor anthracycline derivative and a farnesyl transferase inhibitor of the type described above which has an advantageous inhibitory effect against tumor cell growth, in comparison with the respective effects shown by the individual components of the combination.

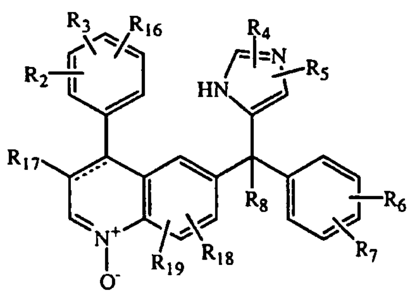
According to the invention therefore we provide a combination of an anti-tumor anthracycline derivative and a farnesyl transferase inhibitor of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) above, in particular a compound of formula (I), (II) or (III):



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl, or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$, wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or

C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),
-O-CH_2-CH_2-O- (a-2),
-O-CH=CH- (a-3),
-O-CH_2-CH_2- (a-4),
-O-CH_2-CH_2-CH_2- (a-5), or
-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl , C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS$(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or
-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),
-S-R^{10} (b-2),
-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-

C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula $-Alk^2-OR^{13}$ or $-Alk^2-NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{19} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

The above described combinations are hereinafter referred to as combinations according to the invention. These combinations may provide a synergistic effect whereby they demonstrate an advantageous therapeutic effect which is greater than that which would have been expected from the effects of the individual components of the combinations.

In Formulas (I), (II) and (III), R^4 or R^5 may also be bound to one of the nitrogen atoms in the imidazole ring. In that case the hydrogen on the nitrogen is replaced by R^4 or R^5 and the meaning of R^4 and R^5 when bound to the nitrogen is limited to hydrogen, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl, C_{1-6}alkylS(O)$_2C_{1-6}$alkyl.

Preferably the substituent R^{18} is situated on the 5 or 7 position of the quinolinone moiety and substituent R^{19} is situated on the 8 position when R^{18} is on the 7-position.

Interesting compounds are these compounds of formula (I) wherein X is oxygen.

Also interesting compounds are these compounds of formula (I) wherein the dotted line

represents a bond, so as to form a double bond.

Another group of interesting compounds are those compounds of formula (I) wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, wherein Alk^1 is methylene and R^9 is C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl.

Still another group of interesting compounds are those compounds of formula (I) wherein R^3 is hydrogen or halo; and R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalomethoxy or hydroxyC_{1-6}alkyloxy.

A further group of interesting compounds are those compounds of formula (I) wherein R^2 and R^3 are on adjacent positions and taken together to form a bivalent radical of formula (a-1), (a-2) or (a-3).

A still further group of interesting compounds are those compounds of formula (I) wherein R^5 is hydrogen and R^4 is hydrogen or C_{1-6}alkyl.

Yet another group of interesting compounds are those compounds of formula (I) wherein R^7 is hydrogen; and R^6 is C_{1-6}alkyl or halo, preferably chloro, especially 4-chloro.

A particular group of compounds are those compounds of formula (I) wherein R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula -$NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, or a radical of formula -Alk^2-OR^{13} wherein R^{13} is hydrogen or C_{1-6}alkyl.

Preferred compounds are those compounds wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, wherein Alk^1 is methylene and R^9 is C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl; R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalomethoxy, hydroxyC_{1-6}alkyloxy or Ar^1; R^3 is hydrogen; R^4 is methyl bound to the nitrogen in 3-position of the imidazole; R^5 is hydrogen; R^6 is chloro; R^7 is hydrogen; R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula -$NR^{11}R^{12}$

wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, or a radical of formula -Alk^2-OR^{13} wherein R^{13} is C_{1-6}alkyl; R^{17} is hydrogen and R^{18} is hydrogen.

Most preferred compounds are
4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-2(1H)-quinolinone,
6-[amino(4-chlorophenyl)-1-methyl-1H-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone;
6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone;
6-[(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone monohydrochloride.monohydrate;
6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone,
6-amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1H)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and
(+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone (Compound 75 in Table 1 of the Experimental part of WO-97/21701) ; or a pharmaceutically acceptable acid addition salt thereof. The latter compound is especially preferred.

Further preferred embodiments of the present invention include compounds of formula (IX) wherein one or more of the following restrictions apply:

- $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9) wherein each R^6 independently is hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, amino or aryl and R^7 is hydrogen;
- $>Y^1-Y^2-$ is a trivalent radical of formula (y-1), (y-2), (y-3), or (y-4) wherein each R^9 independently is hydrogen, halo, carboxyl, C_{1-4}alkyl or C_{1-4}alkyloxycarbonyl;
- r is 0, 1 or 2;
- s is 0 or 1;
- t is 0;
- R^1 is halo, C_{1-6}alkyl or two R^1 substituents ortho to one another on the phenyl ring may independently form together a bivalent radical of formula (a-1);
- R^2 is halo;
- R^3 is halo or a radical of formula (b-1) or (b-3) wherein
  R^{10} is hydrogen or a radical of formula -Alk-OR^{13}.

R^{11} is hydrogen;
R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy or mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl;
Alk is C_{1-6}alkanediyl and R^{13} is hydrogen;

- R^4 is a radical of formula (c-1) or (c-2) wherein
  R^{16} is hydrogen, halo or mono- or di(C_{1-4}alkyl)amino;
  R^{17} is hydrogen or C_{1-6}alkyl;
- aryl is phenyl.

A particular group of compounds consists of those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, $C_{(1-4)}$alkyl or forms a bivalent radical of formula (a-1), R^2 is halo or C_{1-4}alkyl, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2), R^6 is hydrogen, C_{1-4}alkyl or phenyl, R^7 is hydrogen, R^9 is hydrogen or C_{1-4}alkyl, R^{10} is hydrogen or -Alk-OR^{13}, R^{11} is hydrogen and R^{12} is hydrogen or C_{1-6}alkylcarbonyl and R^{13} is hydrogen;

Preferred compounds are those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, preferably chloro and most preferably 3-chloro, R^2 is halo, preferably 4-chloro or 4-fluoro, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2), R^6 is hydrogen, R^7 is hydrogen, R^9 is hydrogen, R^{10} is hydrogen, R^{11} is hydrogen and R^{12} is hydrogen;

Other preferred compounds are those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-2), (x-3) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most preferably 3-chloro or R^1 is C_{1-4}alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4}alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.

The most preferred compounds of formula (IX) are
7-[(4-fluorophenyl)(1H-imidazol-1-yl)methyl]-5-phenylimidazo[1,2-a]quinoline;
α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)-5-phenylimidazo[1,2-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)-imidazo-

[1,2-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)imidazo-[1,2-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo-[1,5-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-1-methyl-α-(1-methyl-1H-imidazol-5-yl)-1,2,4-triazolo[4,3-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo-[1,5-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo-[1,5-a]quinazoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-4,5-dihydro-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo-[1,5-a]quinazoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-N-hydroxy-α-(1-methyl-1H-imidazol-5-yl)-tetrahydro[1,5-a]quinoline-7-methanamine;
α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)-5-(3-methylphenyl)tetrazolo-[1,5-a]quinoline-7-methanamine; the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof.

5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo-[1,5-a]quinazoline-7-methanamine, especially the (-) enantiomer, and its pharmaceutically acceptable acid addition salts are especially preferred.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C_{1-6}alkyl defines straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl and the like; C_{1-8}alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C_{1-6}alkyl as well as the higher homologues thereof containing 7 or 8 carbon atoms such as, for example heptyl or octyl; C_{1-12}alkyl again encompasses C_{1-8}alkyl and the higher homologues thereof containing 9 to 12 carbon atoms, such as, for example, nonyl, decyl, undecyl, dodecyl; C_{1-16}alkyl again encompasses C_{1-12}alkyl and the higher homologues thereof containing 13 to 16 carbon atoms, such as, for example, tridecyl, tetradecyl, pentedecyl and hexadecyl; C_{2-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the

like; C_{1-6}alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof. The term "C(=O)" refers to a carbonyl group, "S(O)" refers to a sulfoxide and "$S(O)_2$" to a sulfon. The term "natural amino acid" refers to a natural amino acid that is bound via a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of the amino acid and the amino group of the remainder of the molecule. Examples of natural amino acids are glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylanaline, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine.

The pharmaceutically acceptable acid or base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. The compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

The compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The terms acid or base addition salt also comprise the hydrates and the solvent addition forms which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX)" is meant to include also the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

Preferred anti-tumor anthracycline derivatives for use in accordance with the invention include daunorubicin, doxorubicin and idarubicin referred to above. Daunorubicin is commercially available for example as the hydrochloride salt from Bedford Laboratories under the trade name Cerubidine, and may be prepared for example as described in patent specification No. 4020270, or by processes analogous thereto. Doxorubicin is commercially available for example as the hydrochloride salt from Astra, and may be prepared for example as described in U.S. patent specification No. 3803124 or by processes analogous thereto. Idarubicin is commercially available for example as the hydrochloride salt from Pharmacia & Upjohn under the trade name Idamycin, and may be prepared for example as described in U.S. patent specification No. 4046878 or by processes analogous thereto Other anti-tumor anthracycline derivatives may be prepared in conventional manner for example by processes analogous to those described above for daunorubicin, doxorubicin and idarubicin.

The present invention also relates to combinations according to the invention for use in medical therapy for example for inhibiting the growth of tumor cells.

The present invention also relates to the use of combinations according to the invention for the preparation of a pharmaceutical composition for inhibiting the growth of tumor cells.

The present invention also relates to a method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination according to the invention.

This invention further provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a combination according to the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g. loss of contact inhibition). This includes the abnormal growth of : (1) tumor cells (tumors) expressing an activated *ras* oncogene; (2) tumor cells in which the *ras* protein is activated as a result of oncogenic mutation of another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant *ras* activation occurs. Furthermore, it has been suggested in literature that *ras* oncogenes not only contribute to the growth of of tumors *in vivo* by a direct effect on tumor cell growth but also indirectly, *i.e.* by facilitating tumor-induced angiogenesis (Rak. J. et al, *Cancer Research*, 55, 4575-4580, 1995). Hence, pharmacologically targetting mutant *ras* oncogenes could conceivably suppress solid tumor growth *in vivo*, in part, by inhibiting tumor-induced angiogenesis.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of a combination according to the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated *ras* oncogene by the administration of an effective amount of combination according to the present invention. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g. adenocarcinoma and including non-small celll lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of

mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carninoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

This invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein *ras* proteins are aberrantly activated as a result of oncogenic mutation in genes, i.e. the *ras* gene itself is not activated by mutation to an oncogenic mutation to an oncogenic form, with said inhibition being accomplished by the administration of an effective amount of a combination according to the invention, to a subject in need of such a treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which *ras* is activated due to mutation or overexpression of tyrosine kinase oncogenes may be inhibited by the combinations according to the invention.

The anti-tumor anthracycline derivative and the farnesyl transferase inhibitor may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular anti-tumor anthracycline derivative and farnesyl transferase inhibitor being administered, their route of administration, the particular tumor being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The farnesyl transferase inhibitor is advantageously administered in an effective amount of from 0.0001 mg/kg to 100 mg/kg body weight, and in particular from 0.001 mg/kg to 10 mg/kg body weight. More particularly, for an adult patient, the dosage is conveniently in the range of 50 to 500mg bid, advantageously 100 to 400 mg bid and particularly 300mg bid.

The anti-tumor anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2, particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2, for daunorubicin in a dosage of about 25 to 45mg/m^2 , and for idarubicin in a dosage of

about 10 to 15 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7,14,21 or 28 days.

It is especially preferred to administer the farnesyl tranferase inhibitor at a dosage of 100 or 200mg bid for 7, 14, 21 or 28 days with a dosage of the anti-tumor anthracycline derivative in the ranges indicated above.

In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the anti-tumor anthracycline derivative and the farnesyl transferase inhibitor may be formulated into various pharmaceutical forms for administration purposes. The components may formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing both components. Farnesyl protein transferase inhibitors can be prepared and formulated into pharmaceutical compositions by methods known in the art and in particular according to the methods described in the published patent specifications mentioned herein and incorporated by reference; for the compounds of formulae (I), (II) and (III) suitable examples can be found in WO-97/21701. Compounds of formulae (IV), (V), and (VI) can be prepared and formulated using methods described in WO 97/16443, compounds of formulae (VII) and (VIII) according to methods described in WO 98/40383 and WO 98/49157 and compounds of formula (IX) according to methods described in WO 00/39082 respectively.

The present invention therefore also relates to a pharmaceutical composition comprising an anti-tumor anthracycline derivative and a farnesyl tranferase inhibitor of formula (I) together with one or more pharmaceutical carriers. To prepare pharmaceutical compositions for use in accordance with the invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration,

tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

It may be appropriate to administer the required dose of each component of the combination as two, three, four or more sub-doses at appropriate intervals throughout the course of treatment Said sub-doses may be formulated as unit dosage forms, for example, in each case containing independently 0.01 to 500 mg, for example 0.1 to 200 mg and in particular 1 to 100mg of each active ingredient per unit dosage form.

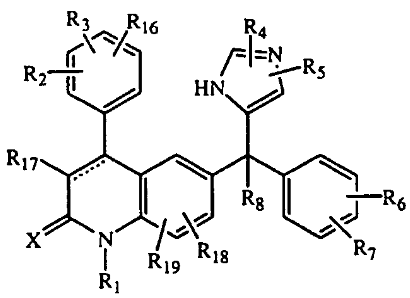
<u>Experimental Testing of Combinations for Inhibition of Tumor Growth</u>

The combinations according to the invention may be tested for their efficacy in inhibiting tumor growth using conventional assays described in the literature for example the HTB177 lung carcinoma described by Liu M et al, Cancer Research, Vol. 58, No.21, 1 November 1998, pages 4947-4956, and the anti-mitotic assay described by Moasser M et al, Proc. Natl. Acad. Sci. USA, Vol. 95, pages 1369-1374, February

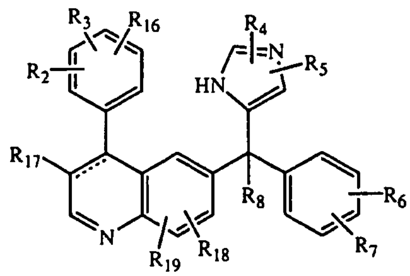
1998. Other *in vitro* and *in vivo* models for determining ant-tumor effects of combinations and possible synergy of the combinations according to the invention are described in WO 98/54966 and WO 98/32114. Clinical models for determining the efficacy and possible synergism for combination therapy in the clinic are generally described in Cancer: Principles and Practice of Oncology, Fifth Edition, edited by Vincent T DeVita, Jr., Samuel Hellman, Steven A. Rosenberg, Lippincott-Raven, Philadelphia, 1997, especially Chapter 17, pages 342-346.

Claims

1. A combination of an anti-tumor anthracyline derivative and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) below:



(I)



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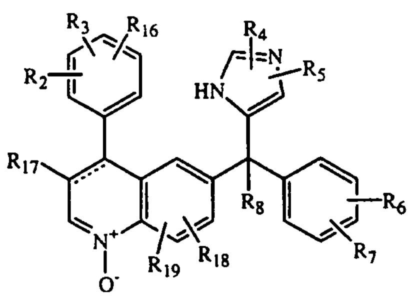


(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-S(O)$_2$-R^9,

wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl,

C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),
-O-CH_2-CH_2-O- (a-2),
-O-CH=CH- (a-3),
-O-CH_2-CH_2- (a-4),
-O-CH_2-CH_2-CH_2- (a-5), or
-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS$(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or
-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),
-S-R^{10} (b-2),
-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or

formula $-Alk^2-OR^{13}$ or $-Alk^2-NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

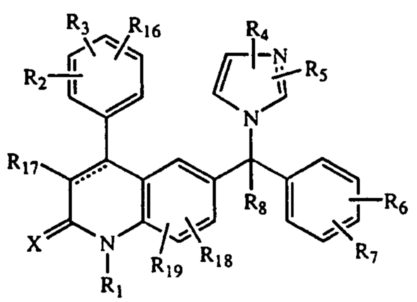
R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

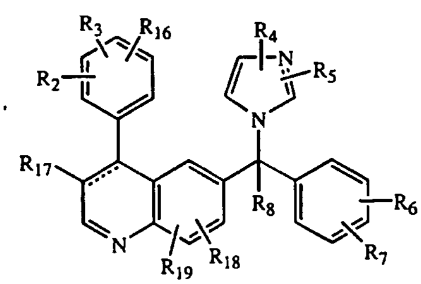
R^{19} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

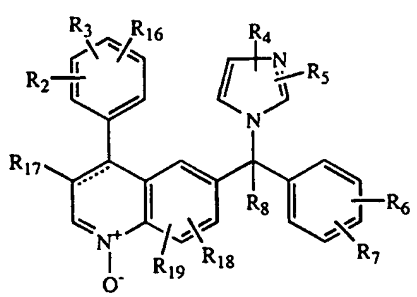
Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.



(IV)



(V)



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or

di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,
or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-S(O)$_2$-R^9,
wherein Alk^1 is C_{1-6}alkanediyl,
R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, amino-C_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^{2}oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl; or
when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH$_2$-O- (a-1),
-O-CH$_2$-CH$_2$-O- (a-2),
-O-CH=CH- (a-3),
-O-CH$_2$-CH$_2$- (a-4),
-O-CH$_2$-CH$_2$-CH$_2$- (a-5), or
-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, Ar^1, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy or Ar^{2}oxy;

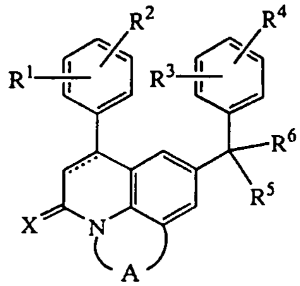
R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl-carbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy-carbonylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, Ar^1, Ar^2C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl;

R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{11} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo;

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.



(VII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

-CH=CH-	(a-1),	$-CH_2$-S-	(a-6),
$-CH_2-CH_2$-	(a-2),	$-CH_2-CH_2$-S-	(a-7),
$-CH_2-CH_2-CH_2$-	(a-3),	-CH=N-	(a-8),
$-CH_2$-O-	(a-4),	-N=N-	(a-9), or
$-CH_2-CH_2$-O-	(a-5),	-CO-NH-	(a-10);

wherein optionally one hydrogen atom may be replaced by C_{1-4}alkyl or Ar^1;

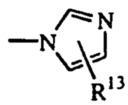
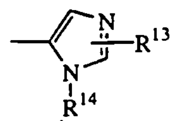
R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^2, Ar^2-C_{1-6}alkyl, Ar^2-oxy, Ar^2-C_{1-6}alkyloxy; or when on adjacent positions R^1 and R^2 taken together may form a bivalent radical of formula

$-O-CH_2$-O-	(b-1),
$-O-CH_2-CH_2$-O-	(b-2),
-O-CH=CH-	(b-3),
$-O-CH_2-CH_2$-	(b-4),
$-O-CH_2-CH_2-CH_2$-	(b-5), or
-CH=CH-CH=CH-	(b-6);

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^3-oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R^3 and R^4 taken together may form a bivalent radical of formula

$-O-CH_2$-O-	(c-1),
$-O-CH_2-CH_2$-O-	(c-2), or
-CH=CH-CH=CH-	(c-3);

R^5 is a radical of formula

 (d-1),  (d-2),

wherein R^{13} is hydrogen, halo, Ar^4, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkyl$S(O)_2C_{1-6}$alkyl;

R^{14} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^5, Ar^5-C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^7 (e-1),

-S-R^7 (e-2),

-N-R^8R^9 (e-3),

wherein

R^7 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^6, Ar^6-C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

R^8 is hydrogen, C_{1-6}alkyl, Ar^7 or Ar^7-C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^8, Ar^8-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^8-carbonyl, Ar^8-C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

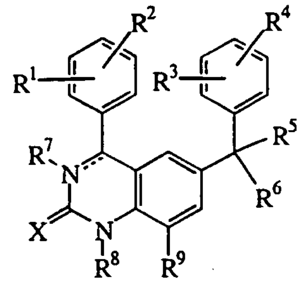
wherein Alk is C_{1-6}alkanediyl;

R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, Ar^9 or Ar^9-C_{1-6}alkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^{10} or Ar^{10}-C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, Ar^{11} or Ar^{11}-C_{1-6}alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.



(VIII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^1C_{1-6}alkyl, Ar^1oxy or Ar^1C_{1-6}alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^{10} (a-1),

-S-R^{10} (a-2),

-N-$R^{11}R^{12}$ (a-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^1carbonyl, Ar^1C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl,

C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino,

or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

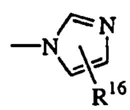
wherein Alk is C_{1-6}alkanediyl;

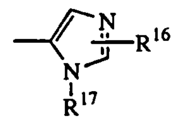
R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^6 is a radical of formula


(b-1),


(b-2),

wherein

R^{16} is hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkyl-$S(O)_2C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^7 is hydrogen or C_{1-6}alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2CH_2 or Het^1CH_2;

R^9 is hydrogen, C_{1-6}alkyl , C_{1-6}alkyloxy or halo; or

R^8 and R^9 taken together to form a bivalent radical of formula

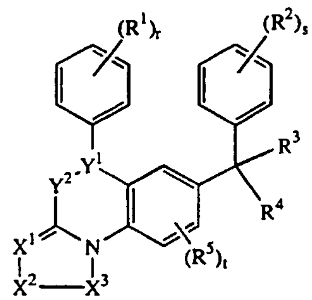
-CH=CH-	(c-1),
$-CH_2-CH_2-$	(c-2),
$-CH_2-CH_2-CH_2-$	(c-3),
$-CH_2-O-$	(c-4), or
$-CH_2-CH_2-O-$	(c-5);

Ar^1 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl;

Ar^2 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

Het^1 is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl

and



(IX)

or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$=X^1-X^2-X^3-$ is a trivalent radical of formula

$=N-CR^6=CR^7-$	(x-1),	$=CR^6-CR^7=CR^8-$	(x-6),
$=N-N=CR^6-$	(x-2),	$=CR^6-N=CR^7-$	(x-7),
$=N-NH-C(=O)-$	(x-3),	$=CR^6-NH-C(=O)-$	(x-8), or
$=N-N=N-$	(x-4),	$=CR^6-N=N-$	(x-9);
$=N-CR^6=N-$	(x-5),		

wherein each R^6, R^7 and R^8 are independently hydrogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkyloxy, aryloxy, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, cyano, amino, thio, C_{1-4}alkylthio, arylthio or aryl;

$>Y^1-Y^2-$ is a trivalent radical of formula

$>CH-CHR^9-$	(y-1),
$>C=N-$	(y-2),
$>CH-NR^9-$	(y-3),or
$>C=CR^9-$	(y-4);

wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxyC_{1-4}alkyl, cyano, carboxyl, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, aryl;

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

each R^1 and R^2 are independently hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, aryl, arylC_{1-6}alkyl, aryloxy or arylC_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminocarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; or

two R^1 or R^2 substituents adjacent to one another on the phenyl ring may independently

form together a bivalent radical of formula

-O-CH$_2$-O- (a-1),

-O-CH$_2$-CH$_2$-O- (a-2),

-O=CH=CH- (a-3),

-O-CH$_2$-CH$_2$- (a-4),

-O-CH$_2$-CH$_2$- CH$_2$- (a-5), or

-CH=CH-CH=CH- (a-6);

R^3 is hydrogen, halo, C$_{1-6}$alkyl, cyano, haloC$_{1-6}$alkyl, hydroxyC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, aminoC$_{1-6}$alkyl, C$_{1-6}$alkyloxyC$_{1-6}$alkyl, C$_{1-6}$alkylthioC$_{1-6}$alkyl, aminocarbonylC$_{1-6}$alkyl, hydroxycarbonyl, hydroxycarbonylC$_{1-6}$alkyl, C$_{1-6}$alkyloxycarbonylC$_{1-6}$alkyl, C$_{1-6}$alkylcarbonylC$_{1-6}$alkyl, C$_{1-6}$alkyloxycarbonyl, aryl, arylC$_{1-6}$alkyloxyC$_{1-6}$alkyl, mono- or di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl;

or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N$R^{11}R^{12}$ (b-3),

wherein

R^{10} is hydrogen, C$_{1-6}$alkyl, C$_{1-6}$alkylcarbonyl, aryl, arylC$_{1-6}$alkyl, C$_{1-6}$alkyloxy-carbonylC$_{1-6}$alkyl, or a radical of formula -Alk-OR^{13} or -Alk-N$R^{14}R^{15}$;

R^{11} is hydrogen, C$_{1-6}$alkyl, aryl or arylC$_{1-6}$alkyl;

R^{12} is hydrogen, C$_{1-6}$alkyl, aryl, hydroxy, amino, C$_{1-6}$alkyloxy, C$_{1-6}$alkylcarbonyl-C$_{1-6}$alkyl, arylC$_{1-6}$alkyl, C$_{1-6}$alkylcarbonylamino, mono- or di(C$_{1-6}$alkyl)amino, C$_{1-6}$alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC$_{1-6}$alkylcarbonyl, arylC$_{1-6}$alkylcarbonyl, C$_{1-6}$alkyloxycarbonyl, C$_{1-6}$alkyloxyC$_{1-6}$alkylcarbonyl, mono- or di(C$_{1-6}$alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C$_{1-3}$alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkylcarbonyl, or a radical or formula -Alk-OR^{13} or -Alk-N$R^{14}R^{15}$;

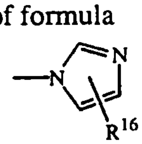
wherein Alk is C$_{1-6}$alkanediyl;

R^{13} is hydrogen, C$_{1-6}$alkyl, C$_{1-6}$alkylcarbonyl, hydroxyC$_{1-6}$alkyl, aryl or arylC$_{1-6}$alkyl;

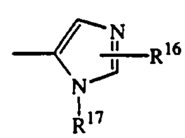
R^{14} is hydrogen, C$_{1-6}$alkyl, aryl or arylC$_{1-6}$alkyl;

R^{15} is hydrogen, C$_{1-6}$alkyl, C$_{1-6}$alkylcarbonyl, aryl or arylC$_{1-6}$alkyl;

R^4 is a radical of formula



(c-1),



(c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, arylC_{1-6}alkyl, trifluoromethyl or di(C_{1-4}alkyl)aminosulfonyl;

R^5 is C_{1-6}alkyl , C_{1-6}alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl .

2. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein X is oxygen and the dotted line represents a bond.

3. A combination as claimed in claim 1 or claim 2 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl or mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl and wherein R^3 is hydrogen and R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalomethoxy or hydroxyC_{1-6}alkyloxy.

4. A combination as claimed in any of the preceding claims wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula -$NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, or a radical of formula -Alk^2-OR^{13} wherein R^{13} is hydrogen or C_{1-6}alkyl.

5. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is selected from:

4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)-methyl]-1-methyl-2(1H)-quinolinone,

6-[amino(4-chlorophenyl)-1-methyl-1H-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-

1-methyl-2(1H)-quinolinone; 6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxy-phenyl)-1-methyl-2(1H)-quinolinone; 6-[(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone monohydrochloride.monohydrate; 6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone, and 6-amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1H)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salts thereof.

6. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chloro-phenyl)-1-methyl-2(1H)-quinolinone; or a pharmaceutically acceptable acid addition salt thereof.

7. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-2), (x-3) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most preferably 3-chloro or R^1 is C_{1-4}alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4}alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.

8. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is 5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine or a pharmaceutically acceptable acid addition salt thereof.

9. A combination as claimed in any of the preceding claims in which the anti-tumor anthracyline derivative is daunorubicin, doxorubicin or idarubicin.

10. A combination as claimed in any of the preceding claims in the form of a pharmaceutical composition comprising an anti-tumor anthracycline derivative and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) (as defined in claim 1) together with one or more pharmaceutical carriers.

11. A combination as claimed in any of the preceding claims for use in medical therapy.

12. A combination as claimed in claim 11 for inhibiting the growth of tumor cells.

13. Use of a combination as claimed in any of claims 1 to 12 in the manufacture of a pharmaceutical composition for inhibiting the growth of tumor cells.

14. A method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination as claimed in any of claims 1 to 12.